Roche

April 23, 2004

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

RE: Docket No. 2003D-0570
Response to FDA request for Input on 1996 Draft Guidance

Reference is made to the Federal Register Notice dated January 26, 2004 (Volume 69, No. 16, pages 3588-3589) requesting comments on the previously published draft guidance entitled "Guidance for the Clinical Evaluation of Weight-Control Drugs". This draft guidance was originally issued September 24, 1996 and provided recommendations for the design and conduct of Phase 1-3 clinical studies aimed at demonstrating the efficacy and safety of Rx weight-loss medications. The Agency is now seeking to incorporate the latest scientific and medical information in the fields of obesity and drug development into an amended obesity guidance document.

In response to the above mentioned Federal Register Notice, Hoffmann La Roche, Inc. is herewith providing input/recommendations to the draft guidance for the clinical evaluation of weight loss drugs. Roche has carefully reviewed the 1996 draft guidance and is providing comments on the following specific issues which we believe should be considered for revision in the future guidance:

1. Indication Population

2. Selected Study Procedures including:
   - Lead-in period for Phase 2 and 3 studies
   - Duration of Phase 3 studies
   - Study population
   -

3. Obesity Related Risk Factors in the Product Label

4. Approval Criteria

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Background:
Roche is an ethical pharmaceutical company with extensive research interests in obesity and related metabolic disorders including diabetes. Roche has considerable experience in the field of obesity having been involved in research and development of potential weight control drugs for over 20 years. These research and development initiatives have resulted in the approval of XENICAL (orlistat), a pancreatic lipase inhibitor, approved for obesity management in the US as well as in over 120 other countries. Roche is the only pharmaceutical company to-date which has opened an IND for a weight loss drug candidate (orlistat) and taken that same drug candidate through both the IND development process and NDA approval process all within the Division of Metabolism and Endocrine Drug Products.

Based on current estimates, there have been over 19 million patient treatments with XENICAL to-date. Roche has conducted over 200 short-term and long-term controlled clinical trials (up to four years duration) assessing the safety and efficacy of potential anti-obesity agents including XENICAL. In addition to this experience in conducting clinical trials for potential weight loss agents, Roche has also conducted extensive focus groups and market research with both physicians whose clinical interests include weight management and treatment of obesity and with overweight and with obese patients. Moreover Roche has been engaged in continuous, ongoing dialogue with the major national and international medical associations, managed care organizations, and with national and international medical experts in the field of obesity and related medical disorders in order to better understand current developments in disease management. These activities have given Roche a broad understanding of obesity and its treatment from several points of view including current thinking in disease management, a good understanding of clinical practice in the treatment of obesity, of reimbursement and payers issues as well as an understanding of patients' needs.

It is against this unique background and knowledge base that Roche is providing the following input in response to the Agency's request for comments on the draft Guidance for the Clinical Evaluation of Weight Control Drugs. This response includes both our recommendations and the scientific/medical rationale for the recommendation addressed in this response.

1. Indication:
The current indication for weight control drugs is for the management of obesity, including weight loss and maintenance of weight loss when used in conjunction with a reduced-calorie diet. Drug candidates are approved for the treatment of obese patients with an initial body mass index of ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia). Clinical trials for investigational weight loss drugs study these target populations in assessing the safety and efficacy of new drug candidates.

In light of the growing obesity epidemic in the US and understanding that, for some overweight patients with BMIs <27 kg/m^2, particularly those patients with one or more obesity related risk factors or with a strong family history of obesity or obesity related risk factors, medical and pharmacologic interventions should be considered to treat as well as possibly prevent or delay patients from progressing to a BMI of 27 or 30 kg/m^2. Such approaches for preventing disease progression and/or for treating the overweight population are consistent with the tenets of the NIH obesity research strategic plan, the recommendations of the American Medical Association, NAASO, and the NHLBI. We believe the future guidance should provide for the evaluation and labeling of potential weight loss agents in such an overweight patient population with BMIs >25 and <27kg/m2. Currently investigational weight loss agents do not study this lower BMI overweight population and physicians have no approved treatment options for such patients despite the acknowledged heath risks of excess body weight in this population as well.

2. Selected Study Procedures

2.a Lead-in Period for Phase 2 and 3 Studies

The lead-in period discussed in the current guidance suggests that patients should be entered into a weight reduction program including diet, behavior modification and exercise prior to being randomized into one of the treatment groups in the controlled clinical trial. After a 6 week lead-in period, if a patient does not lose weight or if weight loss has plateaued, only then should the patient be randomized into the study.

For long-term studies designed to assess the additive efficacy of a pharmacologic agent, this is not an appropriate element of clinical trial design. The purpose of large Phase 3 clinical trials is to determine whether or not a drug is sufficiently efficacious to be a reasonable adjunct to enhance weight loss. To require that the drug can only be studied and therefore only show efficacy when a person can no longer lose weight rather than to improve, extend or continue weight loss appears to be a standard of efficacy that is greater than those for related therapeutic areas. It is well accepted that the best predictor of long-term weight loss is the ability to lose weight during a short-term period. The lead-in period is an aggregate measure of a person's motivation including the ability to understand and maintain a diet and exercise program. As with all complex behavioral changes, there will be a broad spectrum of results. The goal of drug therapy for weight loss is to help patients across the spectrum increase their weight loss efforts and achieve a meaningful weight loss goal. Those who are potential good losers, losing a reasonable amount of weight during a short period of time, can have their ultimate weight loss increased by the drug under investigation while those who are potential poor losers can have the amount of weight they lose potentially increased with the use of the investigational drug treatment. Since the true measure of efficacy for a weight loss drug is the placebo subtracted weight loss difference, the total amount of weight a patient might loss is irrelevant in evaluating the real drug effect. When evaluating the true drug effect, it should make no difference if a person is actively losing weight, if an initial weight loss has plateaued or if a person is

unable to lose any weight at all. Based on Roche's obesity research data from studies conducted with orlistat, the weight loss effect was consistent regardless if patients were losing reasonable amounts of weight with diet and exercise or were resistant to these standard treatments in the lead-in period. In addition, the placebo subtracted weight loss effect of orlistat was similar regardless if the large Phase 3 studies had a placebo lead-in period prior to randomization to the study or if there was no lead-in period.

There is however one reasonable situation in a weight loss study for which a placebo lead-in period may have value and that is in studies with relatively small numbers of patients studied for short periods of time. Since it has been shown that patients who are initially able to lose weight will have greater ultimate weight loss than those who are poor initial losers, it is important to ensure that treatment groups are well balanced with respect to the number of potential good and poor losers. This could be an issue particularly in studies with relatively small numbers of patients studied for short periods of time. If the treatment groups are imbalanced and one group has a greater preponderance of good losers than another treatment group, the conclusion with regard to efficacy could be exaggerated. In larger studies, the randomization process has generally been shown to balance the groups well so that the conclusions with regard to size of the effect are not in doubt.

A final reason for not requiring a lead-in period is that this more closely represents what occurs once a drug is marketed. Patients turn to pharmacologic treatments for many reasons. Certainly some patients will try to lose weight by diet and exercise first, but many obese patients have been unsuccessful in the past and cannot or will not try diet and exercise again without the addition of something that may potentially make these efforts more successful. Studying the drug under actual use conditions will provide for a more realistic estimate of its' true effect and benefits when used in clinical practice.

2.b Duration of Phase 3 Studies

The current draft guidance suggests that prior to approval, drugs for the treatment for obesity need to be studied for 24 months for safety.

Obese patients in general are not inherently at any greater health risk than are patients with other metabolic or chronic conditions, therefore the requirement that the safety of an obesity treatment needs to be studied for two years of continuous treatment prior to approval is unjustified and not consistent with the requirements for many new chemical entities in related therapeutic areas. Unlike chronic treatments for diabetes or dyslipidemia, drugs for the treatment of obesity are frequently used for shorter periods of time. Based on Roche's obesity research program, controlled clinical studies for up to four years of continuous treatment with orlistat, for example, have shown that there were no additional related safety findings identified compared to those which had been identified

after the first year of treatment. Assuming that there are no signals from either pre-clinical evaluations or from shorter term clinical studies, safety in a large population of patients (500-1000) for one year should be sufficient prior to approval to establish a drug's safety profile in most cases. Depending on the mechanism of action of any particular drug, safety evaluations in some populations may have to be longer than a year, but there should be a definitive safety concern that needs to be monitored for longer than one year and in which one year safety evaluations would not suffice to define the safety profile of the drug candidate under clinical investigation. In addition, evaluation of chronic treatments with one year safety data prior to approval is consistent with the tenets of the ICH harmonization process and consistent with the recommendations of NAASO. Safety monitoring of the drug immediately after approval should provide for a far greater ability to detect very uncommon or even rare adverse findings which, as with all other therapeutic areas, generally cannot be detected during a clinical development program regardless of the size and duration.

2.c Study Population

Based on Roche's extensive experience in conducting multiple large Phase 3 clinical trials of one, two and fours years duration in overweight and obese patients, we recommend that Phase 3 study populations should include patients with hypertension, dyslipidemicia, impaired glucose tolerance, and/or metabolic syndrome. We do not recommend however including overweight and obese patients diagnosed and treated for type 2 diabetes in these Phase 3 weight loss studies. We recommend that this population be studied in separate weight loss studies. This recommendation is based on the difference response often observed in this patient population with respect to safety and efficacy, as well as for specific monitoring issues, e.g. a need to adjust diabetic medication to avoid hypoglycemia due to weight loss and improvement in glycemic control.

Roche also recommends that the guidance address the design and efficacy criteria necessary to assess the safety and efficacy of a drug candidate in the treatment of childhood/adolescent weight management. The current draft guidance is silent on recommendations for this important patient population.

3. Obesity Related Risk Factors in the Product Label

The current version of the draft guidance recommends assessing the effect of treatment on obesity-related risk factors in the Phase 3 trials and provides for the inclusion of this data in the label. Roche totally supports maintaining these recommendations in the new guidance. Our extensive interactions and experience with physicians who use pharmacologic intervention in the treatment of their overweight and obese patients, confirms that the effects of treatment on obesity-related risk factors are of great importance in prescriber's benefit/risk assessment for treatment. Therefore we feel it is necessary to not only generate these data in a controlled clinical trial setting but also to include the data in the approved label so that the data are readily accessible to physicians. In addition, it is well

accepted that excess body weight is one of the major underlying causes for the development of type 2 diabetes. Currently approved treatments for type 2 diabetes use the change in HbA1c as the prime efficacy evaluation and the mechanism responsible for the change, while scientifically interesting, is not itself being assessed. Similarly, if a drug produces sufficiently more weight loss than placebo and produces a meaningfully greater decrease in HbA1c, than this should be an indicated use for the drug. The mechanism of action, being weight loss, should not be considered less meaningful than drugs with either unknown mechanisms or other cellular based mechanism that merely lower glucose levels but don't change the key cause of type 2 diabetes, excess body weight.

4. Approval Criteria

The current draft guidance states that there are two key methods for measuring the weight loss efficacy of a compound. The first is to determine if the absolute mean placebo subtracted weight loss difference is at least 5% of the patients' baseline body weight. The second method, also known as the categorical analysis, is to determine if the percentage of patients who reach and maintain a loss of at least 5% of their baseline body weight at the end of 1 year of treatment is significantly greater in patients on drug than on placebo. Roche supports maintaining these criteria but recommends some additional considerations for the categorical analysis approval criteria.

It should be noted that since all patients should also be receiving other supportive interventions such as diet, exercise and possibly behavior modification, both these weight loss criteria are more rigorous than if no adjunctive treatment were be used at all. It is important to show both that background treatment with diet, exercise and placebo did in fact produce a weight loss and that active drug in addition to diet and exercise produced an even greater weight loss.

As presented in detail during the 1997 Advisory committee meeting discussing the approval criteria, for weight control drugs, a weight loss of 5% is considered the level at which clinical benefits are observed and which is consequently one of the most import aims of pharmacologic intervention. This 5% criteria is also supported by several medical associations including NAASO, AMA, ADA and AOA.

However, for some patient populations other considerations must be given when assessing efficacy. Under certain circumstances such as in children and adolescent who are still growing, preventing additional weight gain rather than an actual weight loss is also reasonable criterion for efficacy. It has also been established in clinical studies such as those performed with orlistat in obese and overweight patients with type 2 diabetes, even less weight loss was associated with clinical benefits and improvements in obesity-related risk factors.

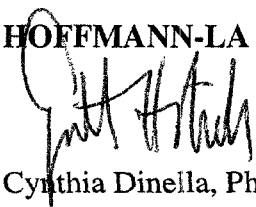
To insure that the incremental effect of drug treatment is confirmed, the second approval criterion could be further defined to specify the required difference between treatment groups in the percentage of patients achieving a 5% weight loss. This would prevent a drug with a too-small difference in response between treatment groups from being considered for approval. For example it would be reasonable to say that the absolute difference between the percentage of patients losing at least 5% of their baseline body weight on drug compared to placebo should be at least 15-20% (as well as being statistically significant). This would mean if 30% of placebo patients lost at least 5% of their bodyweight, then 45-50% of the drug treated patients would need to lose at least 5% of their body weight. These are sufficiently rigorous criteria that, if achieved, would confirm that a drug is very efficacious.

Based on our experience in obesity drug development as well as on numerous and ongoing discussions with medical experts, physicians and patients, Roche believes that the current efficacy guidelines are adequate to define a clinically meaningful weight loss and should be maintained in the revised future guidance. We do believe that, for approval based on the categorical analysis criteria, some consideration could be given in the revised guidance to further define the degree of difference between treatment groups in the percentage of patients achieving a 5% weight loss at the end of one year.

In summary, Roche remains committed to the study of obesity and its management as well as other related therapeutic areas and welcomes the opportunity to comment on this importance guidance. With regard to this response, Roche will be happy to provide additional information on any of the recommendations included in this communication.

Sincerely,

HOFFMANN-LA ROCHE, INC.



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